Changes in cardiac function of rats acutely exposed to nitrogen dioxide were examined by electrocardiographic records. Bradycardia and arrhythmias were observed following exposure to 20 ppm for 3 hours (*76*). These alterations were attributed to changes in parasympathetic nervous activity following exposure. The levels used were high relative to those obtained from unaged tobacco smoke. In addition, it has been suggested that enzyme-inhibiting effects associated with cigarette smoking are due to nicotine N-oxide and nitrogen dioxide. Because thiols are readily oxidized to disulfides by either nitric oxide or nitrogen dioxide, they are potent inhibitors of thiol-dependent enzymes (*116*). In the presence of cigarette smoke, scavenger cells such as macrophages may not be readily activated. In the respiratory system, the major histological sites of damage by nitrogen dioxide are the terminal and respiratory bronchioles and the proximal portions of the alveolar ducts. Nitrogen oxides are also suspected of contributing to the development of pulmonary emphysema (*43*) and the acceleration of platelet aggregation (*101*).

Carbon Disulfide

Epidemiological studies have incriminated carbon disulfide (CS_2) as a factor for the increased risk of arteriosclerotic diseases in workers in the viscose-rayon industry (*39*). The reported acute dose levels of CS_2 during workers' exposure were 20 ppm and higher (*39*). In cigarette mainstream smoke, carbon disulfide can amount to as much as 4 μg per cigarette (*72, 114*). It appears that the sulfur-containing amino acids and proteins and certain pesticides serve as major precursors for CS_2 in tobacco smoke (*15, 72*).

Cadmium

The soil supplies tobacco with traces of cadmium (Cd), which are selectively retained by the plant. Depending on the soil, the Cd in the leaf can amount to a few parts per million (*50*). The mainstream smoke of a blended U.S. cigarette may contain up to 0.2 μg Cd (*97, 102*). In the blood of cigarette smokers, Manthey et al. (*99*) found 2.47 $\pm$ 1.72 μg per liter; Cd levels in the blood of nonsmokers were only 0.43 $\pm$ 0.22 μg per liter. Cd appears to accumulate in the kidney, and has been found in higher concentrations in the kidneys of cigarette smokers than of nonsmokers (*115*).

The potential consequences of increased lifetime exposure to low levels of cadmium are not known. However, autopsy studies have revealed increased cadmium levels in persons with emphysema and hypertension (*131*). Cigarette smoke is known to contain traces of cadmium (0.1 to 0.2 μg per cigarette) (*97, 102*). It is chiefly accumulated in the liver and kidneys, and has been found in levels about twice as high in the kidneys of hypertensive cigarette smokers compared with nonsmokers in the normotensive range (*113*). It is

possible that an increased body burden of cadmium may be related more directly to blood pressure (*108*), although animal studies have implicated genetic differences in susceptibility to cadmium-induced hypertension (*109, 110*). Furthermore, epidemiological studies may be confounded by failure to separate cigarette smokers from drinkers of soft water in determining risk of elevated blood pressure from cadmium intake (*17*).

Cadmium has also been implicated in accelerated atherogenesis and altered lipoprotein patterns in White Carneau pigeons, a species often used to investigate risk factors for arterial disease (*119*). The results of these studies showed that the number and size of atherosclerotic plaques were increased in pigeons given drinking water containing cadmium or lead and that the lipoprotein profile was altered in an independent fashion. The possible mode of action of cadmium on atherogenesis is unknown, but endothelial damage is suggested by the work of Rohrer and colleagues (*121*). In their studies, pregnant rats received a single administration of cadmium (0.5 to 2.0 mg/kg), and vacuoles were observed in the endothelial cells of fetal brains. These vacuoles distorted the shape and orientation of the endothelial cells in the caudate nucleus.

Data on the relation between cigarette smoking and cadmium intake remain inconclusive. Drinking water and genetic factors may overwhelm the effects of cadmium as a cigarette smoke constituent on cardiovascular disease, and more work in this area is necessary before a cause and effect assignment can be made.

Zinc

The average zinc (Zn) content in commercial cigarettes varies between 50 and 80 ppm (*140*) and in the mainstream smoke of U.S. cigarettes between 0.05 and 0.4 μg (*102*). So far, Zn has been determined only in the urine of cigarette smokers, where it occurs in significantly higher concentration than it does in the urine of nonsmokers (*46*). Zinc is a metal component of many important enzyme systems; its availability controls the rate of synthesis of nucleic acids and protein (*98*). In fact, zinc deficiency has been associated with poor growth (*30*), and depressed plasma zinc levels have been used as indicators of myocardial infarction (*94*). In general, low zinc levels have been found to be associated with depressed health status, and supplemental zinc has not been correlated with increased risk of disease development.

Tar

The total particulate matter (TPM) of a cigarette, often referred to as tar, is defined as that portion of the smoke that is retained by a glass fiber filter. This definition is widely accepted and can be regarded as a quantitative approach, since the Cambridge glass fiber

filter retains 99.9 percent of particles of the mainstream smoke that have diameters of ≥ 0.2 μ (*154*). Different methods of smoking cigarettes and of determining tar in the smoke have been applied throughout the world; this needs to be considered when comparing data on cigarette smoke yields in various countries (*28*).

According to the U.S. Federal Trade Commission report of March 1983, the tar yields of commercial U.S. cigarettes vary from <0.5 to 30 mg (*146*). All cigarettes with >20 mg tar yield are nonfilter cigarettes, and practically all cigarettes with tar yields <12 mg are cigarettes with perforated filter tips (*146*). As discussed before, it has to be realized that the standard machine smoking method developed for a comparison of the smoke yields of commercial cigarettes does not reflect the average smoking habits of cigarette smokers, especially of those who smoke low-nicotine cigarettes (*64, 65, 89, 127*). A person's smoking habit is largely dependent on the smoker's need for nicotine. Consumers of low-nicotine cigarettes take larger puff volumes and inhale more frequently than do the smokers of cigarettes with high nicotine yields (>1.0 mg cigarettes) (*64*). At present, the most reliable assay for determining the uptake of particulate matter by an individual smoker is seen in the analysis of nicotine and cotinine in his or her serum (*58*).

In theory, reduction of the toxic components in cigarette smoke should reduce the risk for neoplasms and cardiovascular diseases. Therefore, the introduction of filter cigarettes, which should preclude the inhalation of some of the tobacco tar constituents, would be expected to reduce the incidence of respiratory and cardiovascular dysfunctions. End point analysis of the long-term followup of the Framingham cohort made it possible to test the hypothesis that those who smoke filter cigarettes would be less likely to manifest clinical symptoms of cardivascular disease than would those who smoke nonfilter cigarettes. Despite what seemed a more favorable smoking history, the filter cigarette smokers did not have lower incidence rates of cardiovascular diseases than the nonfilter smokers. This finding was unchanged after multivariate logistic regression analysis to adjust for age, systolic blood pressure, and serum cholesterol (*32*). The relationship of this seemingly negative finding to the tar component of tobacco smoke must remain imprecise because other smoke constituents covary with the tar fraction.

Respiratory complications and immune hypersensitivity have been correlated with intake of particulate phase components of tobacco smoke. Cigarette smokers exhibit greatly increased risks for pulmonary diseases, including emphysema and chronic obstructive lung disease (*144*). Such diseases can also place increased stress on the cardiovascular system. Cigarette smokers demonstrate more frequent macroscopic and microscopic lung abnormalities than do

nonsmokers, with a dose–response relationship being apparent in regard to these changes and the self-reported intensity of smoking.

Research Needs and Priorities

The evidence linking cigarette smoking to cardiovascular diseases is strong. Understanding of the mechanisms whereby cigarette smoking initiates or accelerates disease processes remains imprecise because a variety of smoke constituents exert multiple effects upon body systems.

Epidemiologic studies have correlated increases in atherosclerotic CVD death rates with increased use of cigarettes and also have shown that those persons who stop smoking do in fact exhibit lower death rates than those who continue to smoke. Despite the demonstrated association of smoking with enhanced atherogenesis, risk of coronary death in persons who stop smoking appears to revert to lower levels in a relatively short period following cessation. It is quite likely that the precipitating events leading to thrombus formation and occlusion are decreased, although fibrous plaques will not regress so rapidly (*82*).

Methods for cessation of cigarette smoking, especially among high risk populations, must be a priority in the research endeavor to reduce cardiovascular disease morbidity and mortality. Although termination of the habit is the ideal goal, it must be recognized that this is a difficult task for a number of smokers.

Reduction of the harmful components delivered to the smoker has been another priority objective, aimed at those smokers who will not give up the habit. This task has resulted in the introduction of a variety of low- and ultra-low-yield cigarettes. Whether risks for cardiovascular diseases are truly reduced when these products are used remains to be demonstrated. Several recent studies have shown that smokers alter their smoking behavior when they switch to low-yield cigarettes and can receive increased smoke constituents as they attempt to satisfy a nicotine demand (*64, 65*). This compensatory behavior may lead to accelerated atherogenesis through increased uptake of smoke constituents such as carbon monoxide, hydrogen cyanide, and nitrous oxides. Recently it was reported that the risk of a nonfatal first myocardial infarction in young men was not related to the nicotine or carbon monoxide levels of the cigarette. This could be due to compensatory behavior (*83*).

One should not ignore the proportion of the population that continues to smoke, nor should one accept unchallenged the concept of a "safe" cigarette. The main objective is to reduce the harmful constituents present in tobacco smoke. It is probable that promotion of ultra-low-yield products will not suffice, since compensatory

mechanisms may be triggered by sensory needs for taste as well as for nicotine.

A cigarette considered less harmful for cancer etiology might not reduce the risk for coronary disease. It appears to be a formidable task to develop a product that satisfies the smoker and does not increase disease risk through exposure to carbon monoxide, hydrogen cyanide, nitrous oxide, or still unknown agents.

Of the major cardiovascular risk factors, cigarette smoking is a powerful, prevalent, and potentially correctable contributor that deserves the highest priority among preventive measures to control cardiovascular disease (*82*).

Conclusions

1. Over 4,000 different compounds have been identified in tobacco smoke.
2. Nicotine exerts an effect on ganglionic cells, producing transient excitation. The pharmacological effects are small, but are reinforced several times daily in habitual smokers. The exact mechanisms whereby nicotine might influence cardiovascular events are unknown, but a lowering of the ventricular fibrillation threshold is dose related to nicotine levels.
3. Carbon monoxide may act to precipitate cardiac symptomatology or ischemic episodes in individuals already compromised by coronary disease. In addition, carbon monoxide binds to hemoproteins, potentially inhibiting their functions.
4. Several studies have shown that smokers may alter their smoking behavior when they switch to low-yield cigarettes. This compensatory behavior may lead to the increased uptake of gas phase constituents including carbon monoxide, hydrogen cyanide, and nitrous oxides.
5. It is unlikely that a "safe cigarette" can be developed that will reduce cardiovascular risk.

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SECTION 7. CHANGES IN CIGARETTE SMOKING BEHAVIOR IN CLINICAL AND COMMUNITY TRIALS

Introduction

This section examines the changes in cigarette smoking behavior resulting from intervention strategies. The next section presents detailed data on CHD outcome resulting from these trials compared with those prospective epidemiologic studies for which cessation outcome information is available.

Large-scale primary preventive trials have used both single and multifactorial intervention in high risk populations in an attempt to test the effect of the modification of major risk factors, either alone or in combination, on coronary heart disease (CHD) or respiratory disease. Several of these trials have been developed and implemented since the early 1970s, and provide a valuable opportunity for assessing the efficacy and outcomes of smoking intervention techniques in particular high risk populations and the impact of smoking behavior change on disease. The objective of this section is to present and critically appraise the smoking intervention programs and the smoking cessation outcomes in the large-scale controlled preventive trials.

At present there are two types of preventive trials in cardiovascular or respiratory disease that either have been completed or are currently in progress. One type includes *clinical investigations* in which *individuals* are randomized either to an intervention group for a risk factor reduction program or to their usual source of medical care. These randomized trials are either single factor trials that intervene on one variable such as cigarette smoking, as in the London Civil Servants smoking trial (*55, 60, 61*), or multifactorial trials that generally attempt to change the alterable risk factors of cigarette smoking, hypercholesterolemia, and hypertension, or some combination of these risk factors. In this group are the Göteborg (Sweden) trial (*78, 79, 80*), the Oslo (Norway) study (*16, 17*), and the Multiple Risk Factor Intervention Trial (MRFIT) (*19, 43*).

The randomization of *entire populations* to an intervention or a no-intervention group comprises the second type of trial. In this group of *community investigations* are trials based on random allocation of factories to intervention or regular care, as in the WHO study (*62*), which involves four centers—London, Brussels/Ghent, Rome, and Warsaw—using a common protocol, and trials in which entire geographic areas are randomized, as in the North Karelia project (*52, 53, 54, 63, 64, 65*). Although the Stanford study has been described by its investigators as a community-based investigation (*13, 14, 36, 41*), it did not involve random allocation of communities and thus does not belong in this group as defined here. Although the Stanford group studied three different communities, individuals within one community were randomized to intensive or to community intervention only. Therefore, for the purposes of this review, the

Stanford study will be included with the first group of trials, although it somewhat overlaps both groups.

Smoking intervention methods and smoking behavior change outcomes for each of these trials will be presented and critically evaluated. These prospective studies use experimental design methodology that maximizes comparability of treated and untreated groups by maintaining a high degree of quality control on all aspects of randomization, data collection, and evaluation; by utilizing unbiased statistical treatment of the data; and by detailing a priori specification of the intervention (*38*).

A major problem in assessing outcomes of smoking intervention studies has been research that has often been poor in methodology, quality control, and design. Although preventive trials have generally conformed to the desired methodology as noted above, they too, as with other smoking intervention studies, have been deficient in some of the methods used or in the reporting of the data. The deficiencies of smoking intervention studies have been well reviewed in past investigations (*5, 34, 45, 67*) and will be only briefly summarized here to provide a basis on which to critically review the research and smoking intervention designs in preventive trials.

Problems in Smoking Intervention Studies

Lack of Objective Data to Verify Self-Reported Outcomes

A major deficiency in smoking cessation evaluation research has been the use of self-reported smoking data that have not been validated with objective measures. These data depend on the subjects' honest and accurate reporting and often lead to an overestimation of success, especially among participants who feel the pressure to stop smoking, as in an intervention program. Neaton et al. (*46*) found that when the reported quit-rate of the intervention group in MRFIT was adjusted using serum thiocyanate (SCN) levels, the overreporting ranged from 5 to 9 percent, while a much smaller overreporting rate was found in the usual care group not treated in the program. The demand characteristics of the intervention program may prompt some individuals to falsely comply with the expectations of the interventionist (*2*).

One approach to validation of self-reported data involves the use of serum thiocyanate (SCN) determinations as objective measures of smoking status, with a critical cutoff point used to differentiate smokers from nonsmokers (*3*). SCN is the metabolite of hydrogen cyanide, a pyrrolic product in tobacco smoke. In addition to cigarette smoking, SCN may be elevated by the use of pipes, cigars, or cigarillos. However, the interpretation of SCN concentration is potentially confounded by at least two factors. Certain foods, particularly those of the Brassica genus (cabbage, cauliflower, kale,

kohlrabi, broccoli, brussels sprouts, turnips, and rutabagas), as well as fruit pits and almonds, may elevate levels. Also, diuretics tend to raise SCN levels by an average of 8 μmol/liter (*51*). With such limitations in mind, the biologic half-life of SCN, approximately 14 days (*51*), still makes it a measure well suited for corroboration of self-reports. Determinations of SCN in saliva and urine have also been used and are more adaptable to some settings (*11, 42*). Measurement of carbon monoxide (CO) concentrations in serum or expired air also can be used as a validation tool (*29, 57, 76*). The major drawback of this measure is CO's short half-life of several hours (*56, 72*); it may also be affected by various environmental factors (*72, 77*).

The most specific objective indicator of tobacco use is nicotine itself or its major metabolite cotinine, both of which can be measured in blood, saliva, or urine (*21, 31*). The extremely short half-life of nicotine, on the order of 30 minutes, makes it unsuitable for verification of cessation or for quantifying estimates of tobacco intake, but the 20- to 30-hour half-life of cotinine is much more useful for these purposes (*4, 82*). Unfortunately, cotinine analyses are rarely used in clinical trials because of the expense and the relative unavailability of the complex analytic technique compared with SCN determination.

Lack of Comparison Groups

Only recently have clinical assessments of smoking in intervention programs been more consistent in their use of an experimental design that includes random allocation to the experimental smoking cessation condition or to an appropriate comparison group. Investigators using a minimal treatment or attention–placebo comparison group have demonstrated that these groups produce smoking cessation results beyond those that no intervention would be expected to produce (*28, 32, 37*). These outcomes have been partially accounted for by certain "nonspecific factors" common to all treatment settings and cannot be attributed to a specific intervention technique. These nonspecific factors include the use of self-monitoring, a structured program that promotes the expectation of success, and a therapist's attention (*1, 5, 40*). Determination of the effect of a proposed treatment on outcome results is not possible without rigorous designs that include appropriate experimental controls, preferably a minimal-treatment control group (*37*).

Classification Differences

Smoking control studies use variable criteria for grouping individuals; this makes it difficult to compare outcomes. For example, Straits' (*73*) successes achieved at least an 85 percent reduction in smoking, whereas Keutzer's (*25*) successes achieved at least a 50

percent reduction. Kanzler et al.'s (*23*) "continuing successes" (3 1/2 to 4 years after treatment) were subjects who had not recidivated at any time for "longer than a week," while Ockene et al.'s (*50*) "continuing successes" were at zero cigarettes for at least 2 years, and self-reports were validated with SCN measurements.

Similarly, in some studies a smoker is someone who smokes pipes, cigars, or cigarettes (e.g., Oslo study), while in other studies a subject is classified as a smoker on the basis of whether or not he or she smokes cigarettes only (e.g., MRFIT). Because of the lack of consistency in groups compared and criteria used, outcomes of studies are difficult to evaluate, and cross-validation can provide onflicting outcomes. In order to avoid these problems, standard classification categories have been suggested (*69*).

Followup Differences and Deficiencies

Experimental studies of smoking have used different followup points to assess outcomes and to determine predictor variables. These followup points have included immediately post-treatment (*25*), 2 weeks' post-treatment (*1*), 3-month followup (*22*), 6-month followup (*6*), 1-year followup (*70*), and 3- to 4-year followup (*23, 30, 50*). In most studies, cessation rates at followup points refer to "nonsmoking prevalence" at that point in time, rather than to continued abstinence from immediately post-treatment onward. Such studies give no indication of the dynamics of cessation and relapse that determine the nonsmoking prevalence rate, nor do they indicate what is happening long term with a cohort of smokers. Ockene et al. (*48, 49*), in their analyses of the smoking data from the Multiple Risk Factor Intervention Trial (MRFIT), demonstrate the importance of following cohorts of smokers from baseline to followup points in addition to determining cessation rates at a single point in time. Careful definition of cessation rates should be given in all research reports so that the reader can distinguish whether a given rate refers to a single probe measure or to a quit status of some known duration. Shipley et al. (*71*) have discussed this problem in depth and offered potential standards for reporting in the smoking cessation literature.

Because of the high recidivism rate in the first year of abstinence (*20*), the comparison of a study that measures cessation at immediate post-treatment to one that assesses cessation at 1-year post-treatment will demonstrate very different outcomes. As explained above, the smoker reporting cessation at immediate post-treatment could become either a continuing success or a recidivist at 1-year post-treatment. In effect, comparing stoppers at different points is similar to comparing different groups (*47*). The smoker's continuing susceptibility to relapse, even after being cigarette free for more than 2 years, needs to be reflected in smoking research and intervention by

the inclusion of followup and maintenance programs beyond the usual 6 to 12 months (*49*).

Most studies also fail to note whether a followup point (e.g., 1 year) indicates a period of time since the entire study began or since the smoker entered the program. If it indicates the former, it is possible that there is a different length of followup for participants in the same study, depending on when they entered the program. Outcomes for these participants should not be compared unless appropriate analytic techniques such as life tables (*7*) or person-years (*7*) are used to adjust for the differing lengths of followup.

Methods of Data Reporting

The continuing susceptibility of the smoker to relapse, as well as the fact that it is long-term rather than short-term cessation that has an impact on disease outcomes (*48, 49*), needs to be reflected in the way data are reported in smoking cessation research, although this rarely occurs. Cross-sectional cessation data are generally measured and reported giving little indication of the dynamics of cessation and relapse that determine the cessation rate at any one point in time (*49*). Thus, a cessation rate of 30 percent at 2-year followup does not mean that 30 percent of the smokers in a study remained cigarette free for 2 years. Perhaps only 10 percent were nonsmokers for the entire 2-year period. Studies of smokers quitting both with and without formalized aid show that people often pass through several cycles of cessation and relapse before permanent cessation is achieved (*10, 56*). Analysis of data from cohorts of baseline smokers followed longitudinally provides a more complete understanding of smoking behavior change and "true" long-term cessation. It also provides relevant data for evaluating the effect of cessation on disease outcome. Cohort analyses are missing in all but a very few studies.

The primary evaluation of treatment results should be based on abstinence data for several reasons, as summarized by Pechacek (*75*), including the following: abstinence is the primary goal of most smokers enrolled in programs; smoking behavior change followup data have indicated that most smokers who reduce their smoking without totally stopping return to baseline smoking levels; a clinically insignificant proportion of smokers at followup can be abstinent and yet analyses of rate data can show statistically significant treatment effects; and reports of abstinence rather than reduction are less susceptible to exaggeration and the demands of the program placed on the smoker. In spite of the importance of cessation data and of true long-term data, these are often missing in outcome reports.

The Use of Various Methods for the Determination of Treatment Outcomes

Methods for determining treatment outcomes include telephone calls (*23*), in-person interviews (*19, 70*), and mailed questionnaires (*12*). The variability of the groups of smokers reached by these different methods and their effects changes the criterion groups and can be responsible for an extraneous source of variance leading to distortion of the comparisons. Those subjects who respond immediately to smoking behavior assessment or followup are more often ex-smokers, but those reached only after repeated tries are often smokers (*68*). Therefore, the success and failure groups in a study in which there is a high followup response (*19, 47, 70*) may be quite different from these same groups in a study with a followup response of less than 50 percent (*23*). It would be valuable to pursue a random sample of nonresponders in order to be able to study and compare responders with nonresponders in terms of generalizability of outcomes.

Lack of Information and Precautions Needed to Adequately Interpret Outcomes

A smoking cessation program or trial cannot be adequately evaluated or interpreted without sufficient information about the methods used in the design and implementation of the study, the data included for determination of outcomes, and the methods used for the analysis of the outcomes (*9*). DerSimonian et al. (*9*) surveyed 67 clinical trials reported in 4 well-respected medical journals, and found that only 56 percent were clearly reported with respect to 11 important variables. The 11 variables were selected with regard to their importance in determining the confidence that a reader could place in the author's conclusions, their ability to be discerned by the scientifically literate general medical reader, and their applicability across a variety of medical specialties.

A related point specifically aimed at the clinical trials reviewed in this section is the need to specify all treatments other than smoking cessation (e.g., modification of other risk factors) that participants received. What precautions should be taken comparing smoking cessation results from a trial modifying only smoking behavior to a trial simultaneously modifying several risk factors? Specific as well as nonspecific treatment differences are probably operative on outcomes.

In summary, a critical evaluation of any smoking intervention program needs to consider the deficiencies inherent in the study and data analysis design as well as the deficiencies manifested in the study report by the lack of adequate information. Precautions regarding comparison with other studies and generalizations should also be considered. In the following section, the eight major large-

scale preventive trials implemented since 1970 that include a smoking intervention component and have reported smoking cessation outcomes will be reviewed. (Three-year followup data are available for most of the trials; therefore, whenever possible these data will be presented in addition to whatever other data are available and relevant for comparisons.)

Individual Allocation Trials

Single Factor Controlled Clinical Trials

The London Civil Servants Smoking Trial

The participants in the London Civil Servants smoking trial were drawn from the 16,016 men, aged 40 to 59, who had undergone a cardiorespiratory screening examination in the Whitehall study of London Civil Servants carried out between 1968 and 1970 (*55, 60, 61*). The results of the screening were used to select smokers for the trial who had the highest risk of CHD or chronic bronchitis or both, based on a risk score calculated from the multivariate combination of risk factors (*60, 61*). Men were excluded if they had heart disease, severe hypertension (DBP$>$115 mm Hg), diabetes mellitus, or major concomitant disease; were taking psychotropic drugs; or had a history of previous inpatient psychiatric treatment. The selected men were randomly allocated to an intervention group (IG) or to a "normal care" (NC) group. The results were first sent to the participants' general practitioners, who had the opportunity to withdraw their patients from the study. Random allocation resulted in an intervention group of 714 men and a control group of 731 men (Table 1). The two groups were well balanced on all characteristics measured, with a mean age of approximately 53 years and a mean number of cigarettes smoked of 19 in the two comparison groups.

The smokers randomized to the intervention group were sent a letter inviting them to come and discuss "one or two points personally with a physician" (*58*). This session took about 15 minutes, and the smokers were advised of the health gains of cessation rather than the dangers of continuation and then asked to decide if they wanted further help and support (*58, 59, 60*). Booklets prepared for the study were handed out at this visit. Most men indicated that they would like help and were seen on an average of three more visits in the first 10 weeks, and then at 6 months, with each visit taking about 15 minutes. The only other health advice given was on calorie restriction for those who gained weight. Close contact was maintained over several months, and help was available for those smokers who continued to need it. A special substudy was implemented in which a group of intervention participants were randomly allocated either to the usual procedure of further contact

TABLE 1.—Population, randomization, and baseline smoking data for five major controlled clinical trials

Clinical trial (duration)	Population	Randomization methods/ study groups	Baseline age and smoking data
London Civil Servants Smoking Trial (*60, 61*) (10 years)	1,445 healthy males Aged 40–59 High risk for CHD and/or chronic bronchitis based on risk score	Randomized to smoking intervention or normal care Intervention (IG) = 714 males Normal care (NC) = 714 males	$\bar{X}$ age = 53 $\bar{X}$ cigs = 19
Göteborg (Sweden) Study (*78, 79, 80*) (4 years) (Screening 1970–1974) (Reexamination: 1974–1977)	30,000 males Aged 47–54 Living in Göteborg	Randomized to intervention for smoking, hypertension, hypercholesterolemia, and low physical activity; or to control group Intervention group (IG) = 10,000 males Two control groups (CG) = 20,000 males	$\bar{X}$ age = 51 $\bar{X}$ cigs = ? 65% of 7,455 screened in IG were smokers 16% of IG smoked $\geq$15 cigs/day
Oslo (Norway) Study (*16, 17, 18*) (5 years)	1,232 healthy normotensive males Aged 40–59 Upper quartile CHD risk based on risk score	Randomized to intervention for smoking and cholesterol; or to control group Intervention group (I) = 604 males Control group (C) = 628 males	$\bar{X}$ age = 45 $\bar{X}$ cigs (I) = 12.5 $\bar{X}$ cigs (C) = 13.0 80% were smokers